REMARKS

Entry of the Amendment and reconsideration of the rejection of claims in view of the following Remarks is respectfully requested.

Claim 52 has been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of this claim in one or more continuation applications.

Claims 38 and 50-51 have been amended. Claim 38 has been amended to correct an obvious grammatical error. Claim 50 has been amended, the support for which can be found at page 97, lines 20-26. Claim 51 has been amended to provide antecedent basis. No new matter is added by the amendments.

Applicants have amended the specification to update the priority information.

Withdrawn Rejections

Applicants acknowledge the withdrawal of the rejection of claims 41-55 under 35 U.S.C. 112, second paragraph. Applicants also acknowledge the withdrawal of the rejection of claims 41 and 42 under 35 U.S.C. 112, first paragraph.

Double Patenting

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 30-51 of copending Application No. 09/863,693. As stated in the previous Response, Applicants will consider filing a terminal disclaimer, if appropriate, upon indication of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 47-63 of copending Application No. 09/520,130. As stated in the previous Response, Applicants will consider filing a terminal disclaimer, if appropriate, upon indication of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-29 of copending Application No. 10/143,437. As stated in the previous Response, Applicants will consider filing a terminal disclaimer, if appropriate, upon indication of allowable subject matter.

Written Description

Claims 30-42 have been rejected under 35 U.S.C. §112 second paragraph, as allegedly lacking written description. The Applicants traverse this rejection.

The Examiner contends that the specification only teaches the use of the same light chain in all binding domains in the multispecific antibody. Applicants traverse this rejection.

The fundamental factual inquiry in whether the claims are sufficiently described "is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *MPEP 2163 I.B.* Sufficient written description exists for a claim limitation if one of skill in the art can immediately discern the limitation from reading the original specification. *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 31 USPQ2d 1855 (Fed Cir. 1994). The specification need not, however, describe *ipsis verbis* what is recited in the claims; rather, the claim limitations may be supported in the specification through express, implicit, or inherent disclosure. *MPEP 2163 I.B.* Furthermore, Applicants need not disclose in detail what is conventional or well known to one of ordinary skill in the art. *MPEP 2163 II.A.3(a).* "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." *Id.* It is the Examiner who bears the burden of "providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed." *MPEP 2163.III.A.*

Claims 30-42 are directed to methods of preparing multispecific antibodies comprising a first polypeptide and at least one additional polypeptide, wherein the polypeptides comprise a binding domain comprising a heavy and a light chain, wherein the light chains of the first and additional polypeptides each have three CDR regions, have at least 98% sequence identity, and only differ from one another at amino acid positions outside of the CDR regions. Applicants submit that one of skill in the art at the time of filing would have clearly understood from reading the specification that Applicants were in possession of these claimed methods at the time of filing.

Applicants' invention is directed to methods of generating multispecific antibodies comprising binding domains for more than one antigen. Applicants have disclosed that paired

light chains having at least 98% sequence identity can very likely be found for any V_L comparison (page 97, lines 6-9). Applicants have disclosed the panning of a large human scFv antibody library for antibodies specific for eleven different antigens that represent considerable variation in structure and function (page 95, line 27 through page 96 line 9). After comparing the V_L sequences of the antibodies, Applicants discovered at least one, and often more than one, light chains having at least 98 % sequence identity for most pair wise comparisons (page 96, line 21 through page 97, line 26, Table 6, Appendix, Figure 4 and Figure 8). Based upon these results, it is likely that light chains that have at least 98% sequence identity can be found for any V_L comparison. Therefore, the Applicants have demonstrated that light chains that bind to two different antigens need not have 100% identity.

The Examiner contends, however, that the present specification does not contemplate multispecific antibodies comprising light chains having even 1 amino acid difference between them, because the specification allegedly only discloses comparing light chains to identify a single common light chain for use in a multispecific antibody.

The Applicants respectfully disagree, and submit that the specification does disclose the use of light chains having less than 100% identity, for example, having at least 98% identity. As stated in the previous Response, the specification discloses two light chains that have 98% sequence identity and differ by two residues outside of the antigen binding CDRs (page 97, line 24 to page 98, line 3. The specification states that these two amino acid changes may have little or no effect on antigen binding (page 97, lines 26-27). The specification concludes that, while the sequence similarity of these light chains makes them candidates for the common light chain of the invention, in an alternative embodiment "according to the invention, such light chains having 98-99% sequence identity with the light chain of a prospective paired scFv (Axl. 78, for example), *may be substituted with the paired light chain and retain binding specificity*" (page 97, line 28 through page 98, line 3) (emphasis added). Therefore, the present specification teaches that light chains having at least 98% sequence identity can be utilized in multispecific antibodies, without having an effect on antigen binding. Applicants respectfully submit, therefore, that one of skill in the art would readily apprehend that Applicants were in possession of multispecific antibodies comprising light chains having at least 98% identity.

In response, however, the Examiner states that the cited portion of the specification is directed to identifying a single light chain, and the present claims are therefore not supported.

Applicants respectfully disagree for the reasons discussed above. Furthermore, the Applicants reiterate that the specification need not describe *ipsis verbis* what is recited in the claims. While Applicants do not agree with the Examiner's position and contend that there is explicit support for the claim, Applicants also submit that the specification need not explicitly describe every nuance of the claim; rather, the claim limitations may be supported in the specification through implicit or inherent disclosure. As noted above, it is the Examiner's burden to show why one of skill in the art would not have recognized that the specification implicitly supports the claims. As discussed above, the specification expressly discloses that for any given pair of antigens, two light chains having at least 98% sequence identity can very likely be found, each of which can bind to either antigen. The specification expressly exemplifies multiple examples of light chains found to have at least 98% sequence identity, and each of which can bind to either of two antigens. The specification expressly discloses that light chains having 98-99% sequence identity can be substituted, in an alternative embodiment of the invention, with the light chain of a prospective paired scFv, and that the amino acid changes between them may have little or no effect on antigen binding.

The Applicants respectfully submit that while the Examiner has contended that the specification does not expressly provide support for common light chains having even one amino acid difference, the Examiner has not articulated any reason as to why the disclosure does not, at the very least, implicitly support such light chains.

Applicants respectfully submit that claims 30-42 are amply described in the specification for at least the foregoing reasons. Furthermore, since the claims as amended are fully described by the specification, Applicants submit that no new matter was added by the amendments. Withdrawal of the rejection is respectfully requested.

Claims 50 and 53-55 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description. The Examiner contends that the claims should recite that the common light chain differs only outside of the CDRs. Although the Applicants do not agree with the propriety of this rejection, in order to expedite prosecution, claim 50 now recites that the common light chain has at least 98% sequence identity to each variable domain of a light chain of a first antibody and at least one additional antibody, and only differs from the first and at least one additional antibody at amino acid positions outside of the CDR regions. Withdrawal of the rejection is requested.